Residual viremia and viral blips in the modern cART era: a glimpse beneath the surface

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Background

- Viral blips are a common phenomenon in HIV treatment, though their aetiology remains uncertain.
- One explanation could be that blips are preceded by relatively high levels of residual viremia (RV) and are caused by variations around this higher set point.
- It is unknown what modifiable factors are associated with this virologic set point.
- Previous research has shown that integrase inhibitor (INSTI)-based therapy was associated with lower blip incidences compared to protease inhibitors (PIs) or non-nucleoside reverse transcriptase inhibitors (NNRTIs).[1]
- Therefore, we hypothesized that RV is associated with the type of antiretroviral anchor and the occurrence of blips.

Aims

1) To investigate whether the type of antiretroviral anchor is associated with RV
2) To investigate whether RV is associated with the occurrence of blips

Methods

- All treatment courses in 2010-2020 consisting of 2 nucleos(-t)ide reverse transcriptase inhibitors and 1 anchor in virologically suppressed people living with HIV (PLWH) were evaluated for:

- **RV**: viral loads (VLs) with detectable viremia <50 cop/mL. Groups (Fig. 1):
  - RNA$^-$ (no RV)
  - RV RNA$^+$ <20 cop/mL
  - RV 20-49 cop/mL
- **Blips**: isolated VLs 50–499 cop/mL between measurements <50 cop/mL.

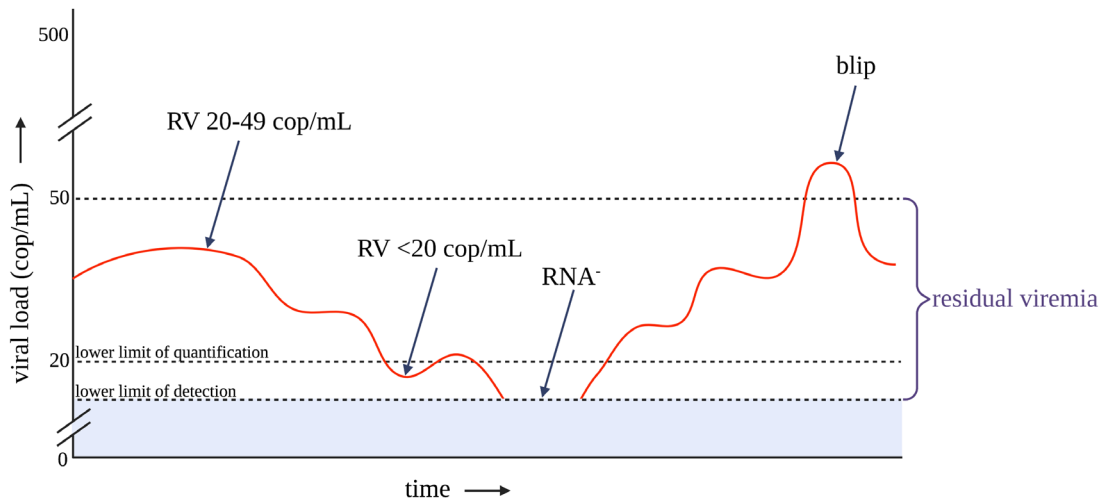

Figure 1. Visual representation of VL limits for RV, RNA$^-$ and blips[†]

- If VLs >50 cop/mL were deemed to result from non-adherence, based on the documented conclusion of the treating physician in the medical records, the course was excluded from analysis.

Statistical Analysis

- Associations were investigated using multivariable generalized linear mixed models using a random intercept and slope for time per individual.
- Multiple Imputation was used in case of missing data.

Confounders:
- Time-varying (per VL): cART anchor, age at VL, time since ART initiation.
- Time-independent: Sex, Fiebig stage at ART initiation, lowest available CD4$^+$ count, zenith VL.

Results

A total of 23,596 VLs from 1658 PLWH were analyzed. The median age at study entry was 43.32 years (interquartile range: 35.04 – 51.26) and 1341 (80.9%) were male.

VLs per antiretroviral anchor:

- INSTIs → 5082 VLs (21.5%)
- PIs → 8568 VLs (36.3%)
- NNRTIs → 9946 VLs (42.2%)

VLs per outcome:

- Blips → 332 VLs (1.4%)
- RNA$^-$ → 15,326 VLs (65.0%)
- RV <20 cop/mL → 6318 VLs (26.8%)
- RV 20-49 cop/mL → 1620 VLs (6.9%)

Antiretroviral anchor and RV:

- Compared with INSTIs, PIs had significantly higher odds of RV (OR 1.29) whereas NNRTIs had lower odds (OR 0.76) (Table 1).
- The time since ART initiation, Fiebig stage VI (*vs.* I-V), lowest available CD4$^+$ count and Zenith VL were also found significantly associated with RV.

RV and occurrence of blips:

- Preceding RV <20 cop/mL and 20-49 cop/mL (*vs.* RNA$^-$) were significantly associated with a 2.72 and 5.00 higher odds of a blip, respectively.
- PLWH with a Zenith VL ≥1,000,000 cop/mL (*vs.* <10,000) also had significantly higher odds of viral blips.

Table 1	Occurrence of blips		Level of residual viremia*	
	OR (95% CI)	p-value	OR (95% CI)	p-value
Time since study inclusion (per year increase)	0.87 (0.78 - 0.98)	**0.02**	0.88 (0.86 - 0.90)	**<0.001**
Female sex (*vs.* male sex)	0.90 (0.61 - 1.31)	0.56	0.90 (0.77 - 1.05)	0.17
Age (per year increase)	1.02 (0.89 – 1.19)	0.76	1.00 (1.00 - 1.00)	0.36
cART anchor				
- INSTI	-[††]	-[††]	1	-
- PI	-[††]	-[††]	1.29 (1.15 - 1.44)	**<0.001**
- NNRTI	-[††]	-[††]	0.76 (0.68 - 0.85)	**<0.001**
Time since ART initiation (per year increase)	0.97 (0.94 - 1.00)	0.06	0.95 (0.94 - 0.96)	**<0.001**
Fiebig stage VI at ART initiation (*vs.* stage I-V)	1.99 (0.66 - 6.05)	0.23	1.51 (1.04 - 2.20)	**0.03**
Lowest available CD4$^+$ count (per 10 cell/mm^3 increase)	1.00 (0.99 - 1.01)	0.56	0.99 (0.99 – 1.00)	**<0.001**
Zenith VL cop/mL				
- <10,000	1	-	1	-
- 10,000-99,999	2.03 (0.66 - 6.23)	0.22	2.10 (1.54 - 2.85)	**<0.001**
- 100,000-999,999	2.80 (0.90 - 8.76)	0.08	3.49 (2.59 - 4.70)	**<0.001**
- ≥1,000,000	5.16 (1.54 - 17.29)	**0.01**	5.40 (3.59 - 8.13)	**<0.001**
Residual viremia cop/mL				
- RNA$^-$	1	-	-	-
- RV <20 cop/mL	2.72 (2.03 – 3.67)	**<0.001**	-	-
- RV 20-49 cop/mL	5.00 (3.49 – 7.17)	**<0.001**	-	-

Conclusions:

- In this large cohort, we show that viral blips are associated with high preceding levels of RV.
- Among several other factors, NNRTI- and INSTI-use was associated with lower RV levels compared with PIs.
- These findings suggest blips having a multifactorial origin, with RV attributable to anchor type partially contributing to this phenomenon.
- Finally, the viral characteristics associated with RV and blips suggest a role for the reservoir.

References
1. Dijkstra et al. *JAIDS* 2022

[†] Figure created with BioRender.com.
[††] As the variable 'cART anchor' is in the causal pathway as a precursor for the association between residual viremia and the occurrence of viral blips, it was not included in the regression.
Abbreviations: ART, antiretroviral therapy; cART, combination antiretroviral therapy; CI, confidence interval; cop, copies; INSTI, integrase strand transfer inhibitor; NNRTI, non-nucleoside reverse transcriptase inhibitor; OR, odds ratio; PI, protease inhibitor; VL, viral load.